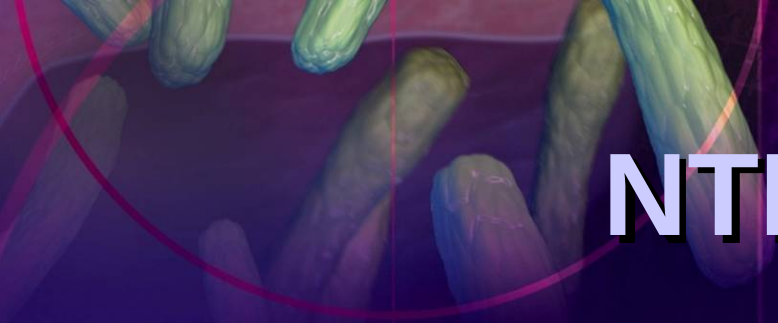


NTM Clinical

Who is your suspect and who to treat?

Epidemiology and Clinical Management

Kevin L. Winthrop, MD, MPH
Professor, School of Public Health
Oregon Health & Science University

Disclosures

- NTM Research funding
  - US Federal Drug Administration (FDA)
  - Insmed
  - NTMir
  - Patient Centered Outcomes Research Institute (PCORI)

NTM Disease Manifestations

84% of NTM disease is MAC

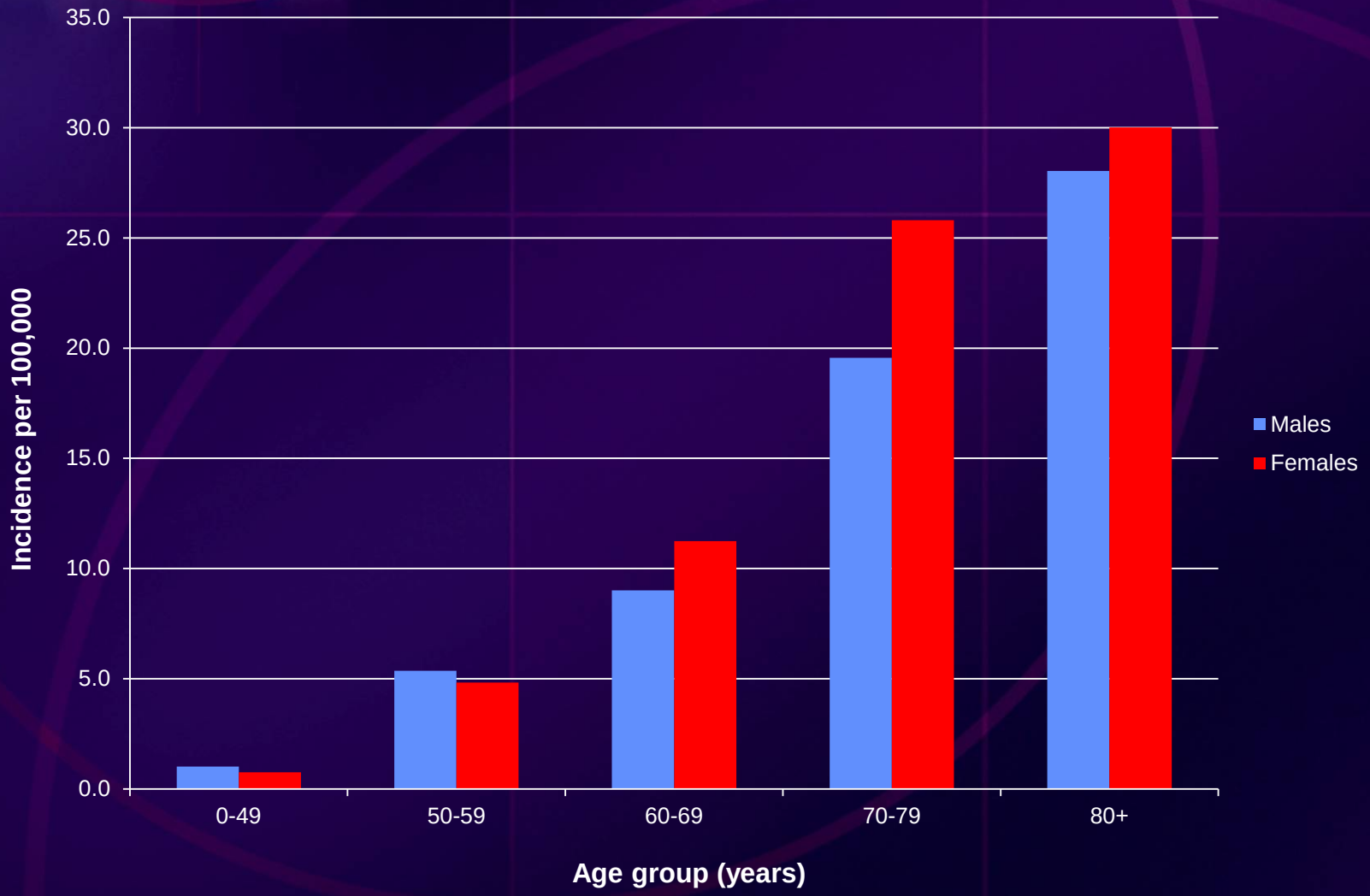
Table 2. Nontuberculous mycobacterium (NTM) cases by species and disease site, Oregon 2007-2012

Mycobacterium species	Pulmonary	Skin/ soft tissue	Disseminated	Lymph	Other	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
M. avium/intracellulare complex	1005 (92.8%)	68 (37.8%)	35 (79.5%)	21 (87.5%)	42 (60%)	1171 (83.6%)
M. abscessus/chelonae complex	46 (4.2%)	51 (28.3%)	1 (2.3%)	1 (4.2%)	9 (12.9%)	108 (7.7%)
M. fortuitum/ mucogenicum	5 (0.5%)	21 (11.7%)	2 (4.5%)	1 (4.2%)	3 (4.3%)	32 (2.3%)
M. marinum	-	17 (9.4%)	-	-	2 (2.9%)	19 (1.4%)
M. lentiflavum	6 (0.6%)	1 (0.6%)	-	-	-	7 (0.5%)
M. kansasii	5 (0.5%)	-	-	-	1 (1.4%)	6 (0.4%)
M. bovis	-	1 (0.6%)	-	-	3 (4.3%)	4 (0.3%)
M. goodii	-	4 (2.2%)	-	-	-	4 (0.3%)
M. xenopi	2 (0.2%)	1 (0.6%)	-	-	1 (1.4%)	4 (0.3%)
M. aubagnense	-	1 (0.6%)	1 (2.3%)	-	1 (1.4%)	3 (0.2%)
M. alvei	-	2 (1.1%)	-	-	-	2 (0.1%)
M. immunogenum	1 (0.1%)	-	-	-	1 (1.4%)	2 (0.1%)
Other (unspeciated and 13 species with a single case)	13 (1.2%)	12 (6.7%)	5 (11.4%)	1 (4.2%)	7 (10%)	38 (2.7%)
TOTAL	1083	180	44	24	70	1401

77% of NTM disease is pulmonary

Henkle E, et al. (abstract) ATS 2014

Annual age- and sex- specific incidence of pulmonary NTM disease in Oregon, 2007-2012

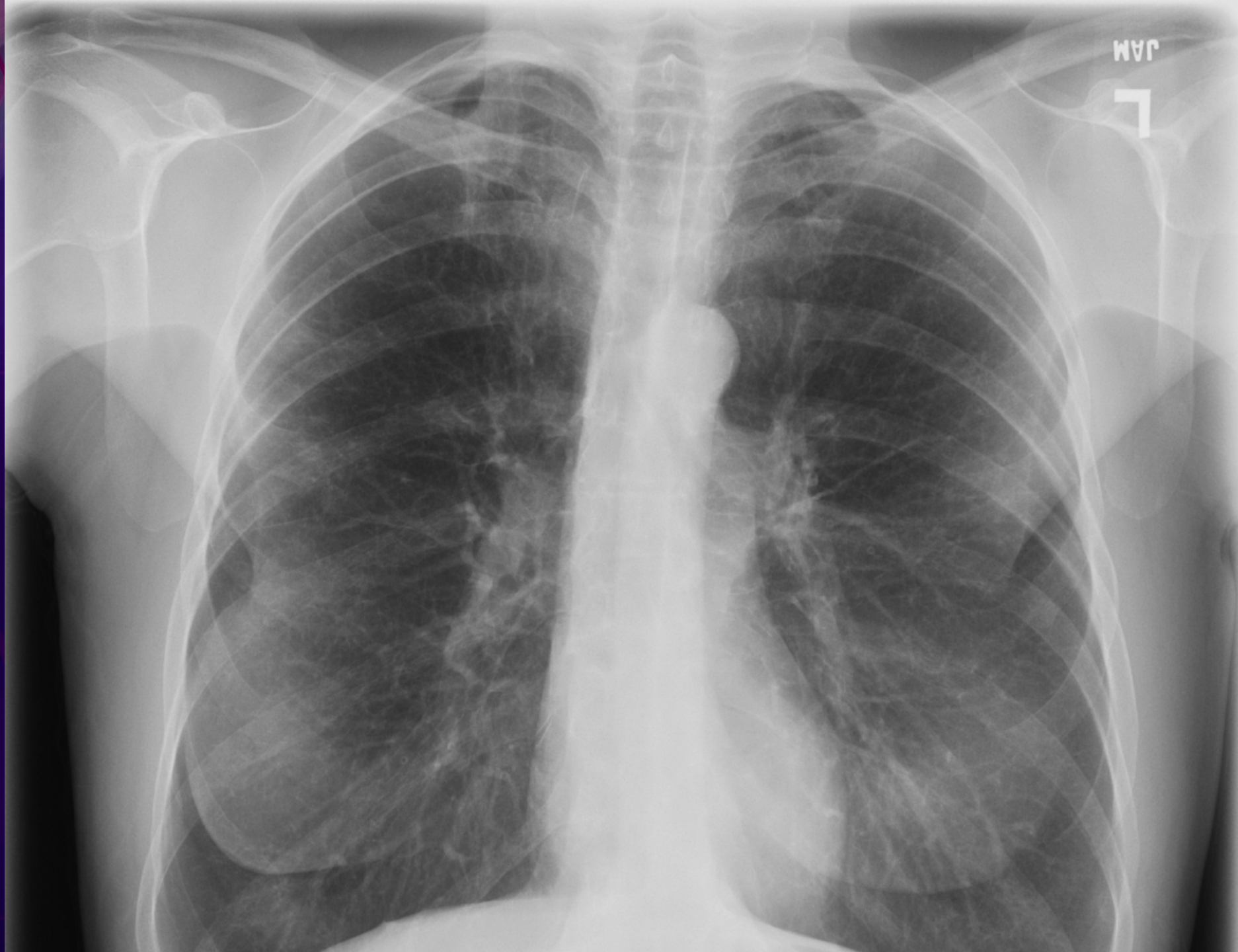


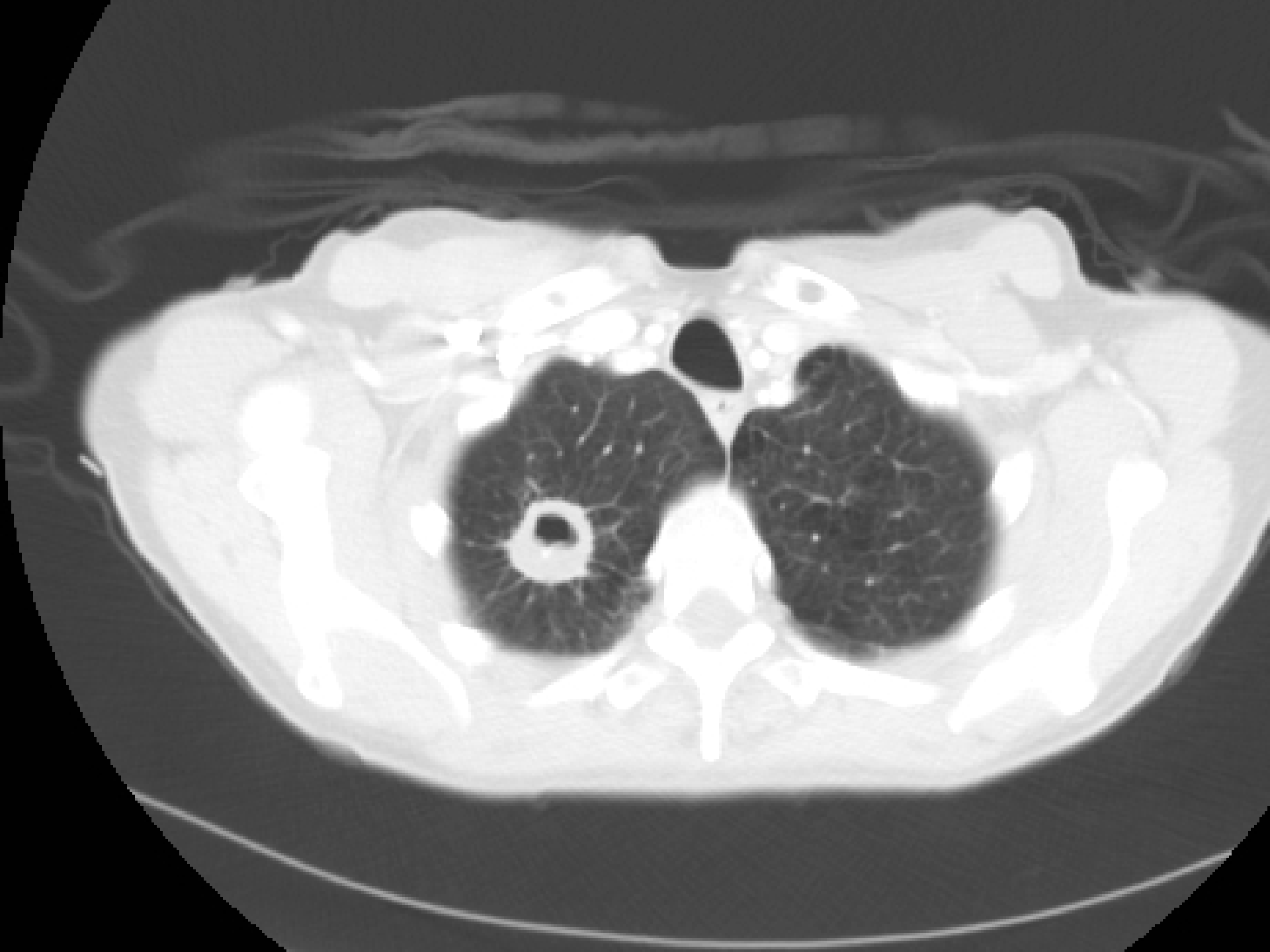
Two Disease Types

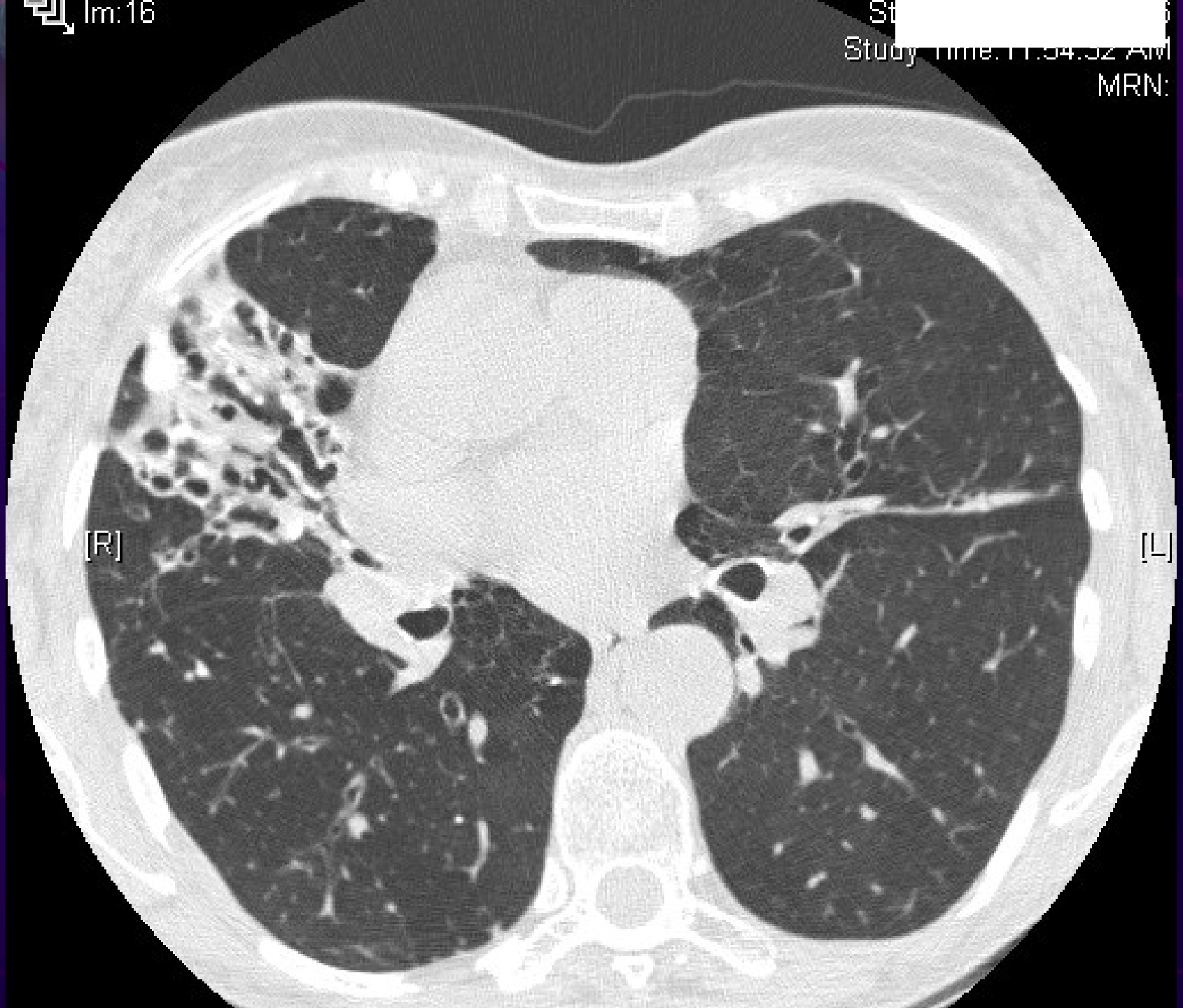
- Older male, smoker, COPD
  - Apical cavitary or fibronodular disease
  - More rapidly progressive

- Older female (“Lady-Windermere”)
  - Scoliosis, thin, pectus deformities*, hypomastia, mitral valve prolapse
  - Nodular and interstitial nodular infiltrate
  - Bronchiectasis right middle lobe / lingula
  - Bronchiolitis (“tree and bud”) on HRCT
  - Slowly progressive

*Iseman MD et al. *Am Rev Respir Dis.* 1991


MAL

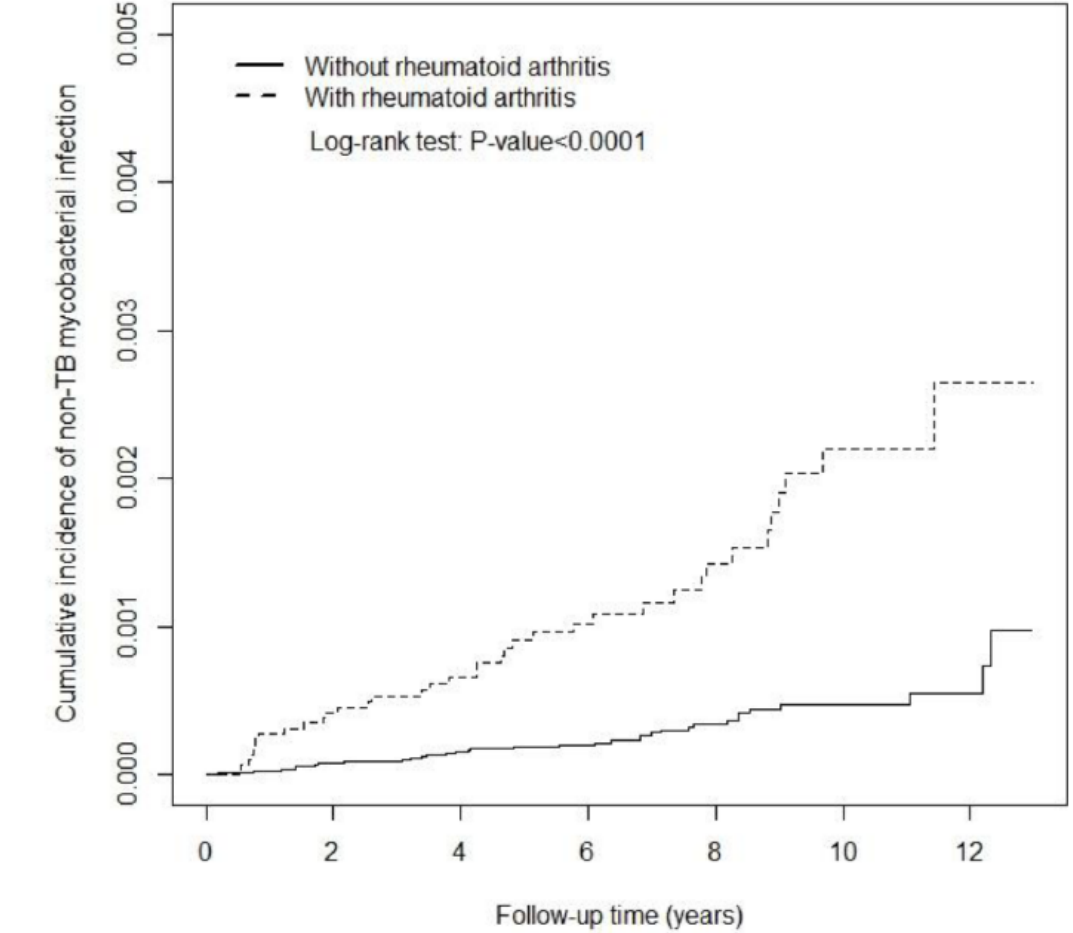



Im:16
MRN:
[R]
[L]

Risk Factors for Pulmonary NTM

- Underlying lung architectural abnormalities
  - Bronchiectasis, cystic fibrosis
  - Alpha-one antitrypsin, emphysema
  - Prior TB or other infection
  - GERD with micro-aspiration
- Exposure/transmission information lacking
  - Gardening?
  - Hot tubs?

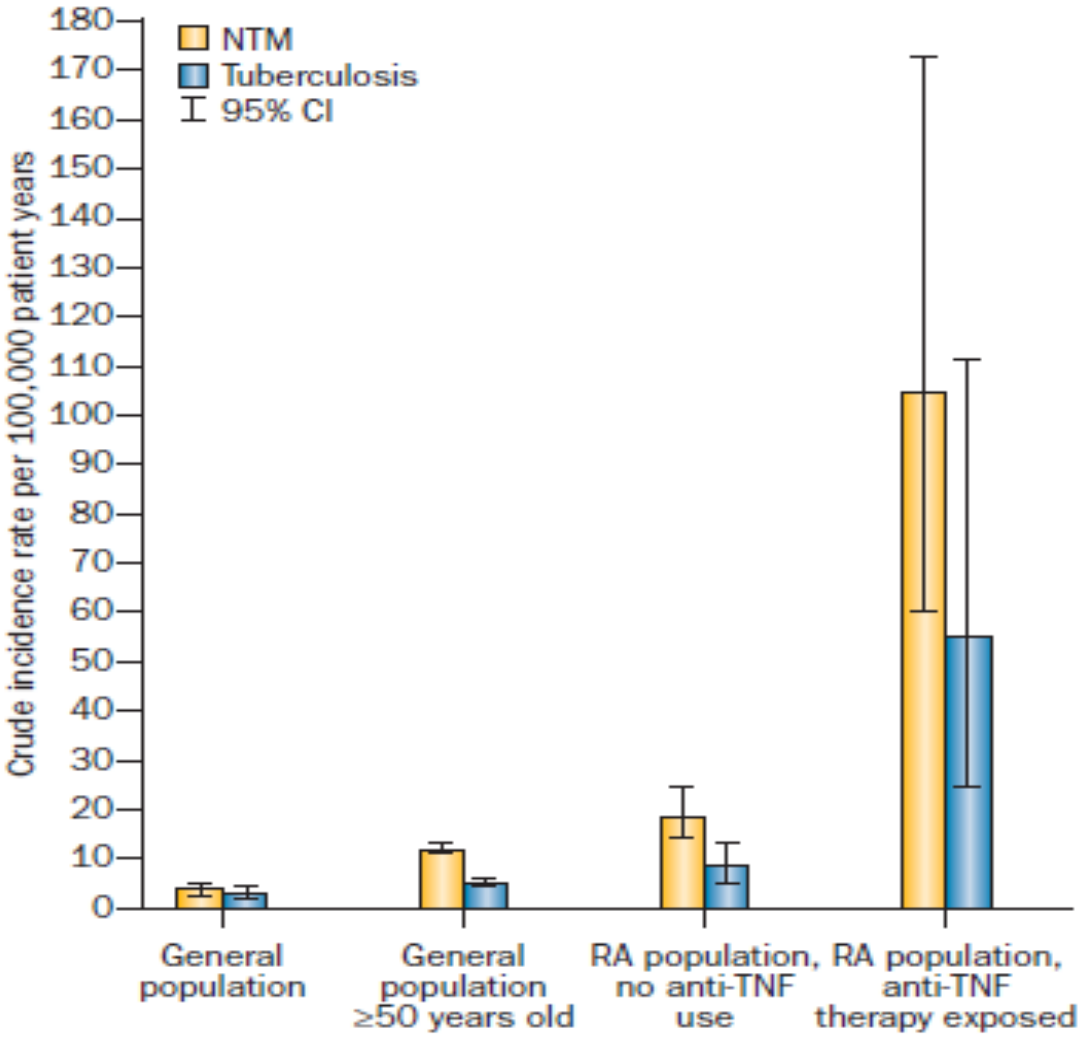
RA is risk factor for NTM



NTM risk among RA 4.1 X higher (Taiwan)

Yeh JJ et al. Plos One 2014

Figure 2



Winthrop KL et al. Ann Rheum Dis 2013; Winthrop KL Nat Rheum Rev 2013

Steroids and Pulmonary NTM

- Case-control study in Oregon and Washington
  - OR = 8.0 for prednisone use
- Denmark COPD cohort
  - Inhaled corticosteroids (ICS) RR 1.24
- Japanese case-control study
  - ICS duration and dose associated with NTM among asthmatic
- In all three studies
  - Higher risk of NTM with oral prednisone doses >15 mg and >800 mg fluticasone equivalent.

Dirac MA et al. AJRCCM 2012; Hojo M et al. Respir 2012; Andrejak C et al Thorax 2013

MAC Therapeutic Options

- **Diagnosis ≠ decision to treat**
  - Observation vs. suppression vs. cure
- Treatment best defined for MAC
  - **Macrolide, rifampin, ethambutol**
  - **Amikacin** (parenteral or inhaled PRN)
  - 18-24 months (12 month culture negative)
  - No macrolide monotherapy
  - **TIW okay** if non-cavitary or not re-infection

Griffith DG, et al. AJRCCM 2007

The Griffith Frustration Index (GFI)

- **NTM respiratory pathogen**
  - ***M. kansasii***
  - ***M. szulgai***
  - ***M. xenopi***
  - **MAC**
  - ***M. malmoense***
  - ***M. abscessus***
  - ***M. simiae***

Frustration Index (GFI),

1 (no problem)-10 (big problem)

- **1**
- **3**
- **5-6**
- **5-6**
- **5-6**
- **8-9**
- **10+**

M. abscessus Parenteral Drugs

- "Cure" = rare (often treat off and on forever)
- Limited antibiotic options based upon susceptibility testing
- Parenteral agents
  - Tigecycline 50mg daily
  - Cefoxitin 2gm TID,
  - Imipenam 500-1000mg BID
  - Amikacin 10mg/kg TIW

Therapeutic Unmet Need

- Efficacy
  - “cure” is unusual
- Tolerability
  - High degree of non-serious adverse events
  - Often “lose” at least 1 drug during initial therapy
  - Serious adverse events (e.g. optic neuritis)

Drug-Drug Interactions

- Rifampin
  - Beta-blockers, Levothyroxine, CA2+ blockers, warfarin, anti-platelet therapies
  - Tacrolimus, steroids, cyclosporin
  - Azoles, Protease inhibitors, FQs
- Azithromycin
  - Digoxin, warfarin
- Clarithromycin has many of the above
- QT issue
  - Clari/azi, FQs, Bedaquiline, Clofaz, others

Amikacin Resistance (MAI)

Initial amikacin MIC (μg/ml)	No. of isolates	Cumulative % of isolates
<1	7	1.5
2	18	5.4
4	57	17.7
8	144	48.9
16	171	85.9
32	46	95.9
64	9	97.8
>64	10	100

16S RNA gene A1408G mutation

[a] These data were determined with the CLSI-approved broth microdilution method (4).
[b] MIC mode, 16 μg/ml; MIC_{50}, 16 μg/ml; MIC_{90}, 32 μg/ml.

Brown-Elliott B, et al *J Clin Microbiology* 2013

ANNALSATS SUPPLEMENT

Patient-Centered Research Priorities for Pulmonary Nontuberculous Mycobacteria (NTM) Infection

An NTM Research Consortium Workshop Report

Emily Henkle[1], Timothy Aksamit[2], Alan Barker[3], Charles L. Daley[4], David Griffith[5], Philip Leitman[6], Amy Leitman[6], Elisha Malanga[7], Theodore K. Marras[8], Kenneth N. Olivier[9], D. Rebecca Prevots[10], Delia Prieto[7], Alexandra L. Quittner[11], William Skach[12], John W. Walsh[7], Kevin L. Winthrop[13], and the NTMRC Patient Advisory Panel

[1]School of Public Health, Oregon Health & Science University–Portland State University, Portland, Oregon; [2]Pulmonary Disease and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota; [3]Pulmonary Critical Care Medicine, Oregon Health & Science University, Portland, Oregon; [4]Department of Medicine, National Jewish Health, Denver, Colorado; [5]University of Texas Health Science Center, Tyler, Texas; [6]NTM Info & Research, Miami, Florida; [7]COPD Foundation, Washington, DC; [8]Department of Medicine, University of Toronto, Toronto, Ontario, Canada; [9]Cardiovascular and Pulmonary Branch, National Heart, Lung, and Blood Institute, National Institutes of Health (NIH), Bethesda, Maryland; [10]Laboratory of Clinical Infectious Disease, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; [11]Department of Psychology, University of Miami, Coral Gables, Florida; [12]Cystic Fibrosis Foundation, Bethesda, Maryland; and [13]Division of Infectious Diseases, Public Health, and Preventive Medicine, Oregon Health & Science University, Portland, Oregon

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Cynthia Flora
Marge Gustafson
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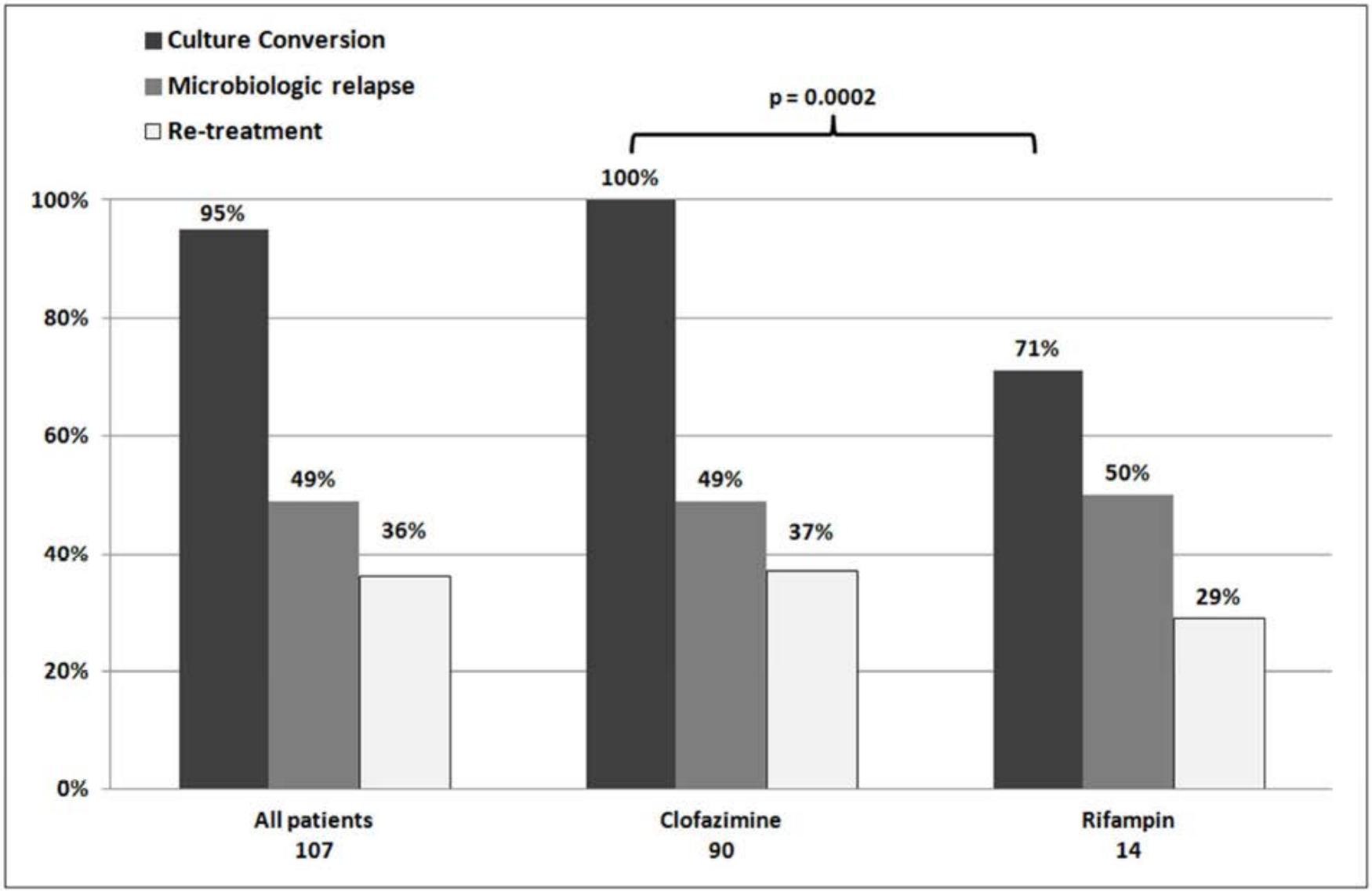
Matthew Pozsgai
Mary Pozsgai
Margery Stalch
Sue Tsang

Ann Am Thorac Soc Vol 13, No 9, pp S379–S384, Sep 2016

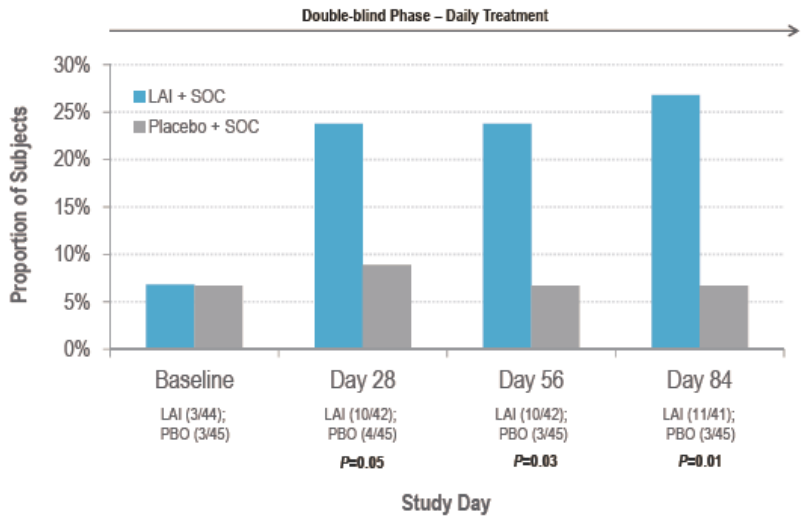
Clofazimine



Jarand J et al. Chest 2015

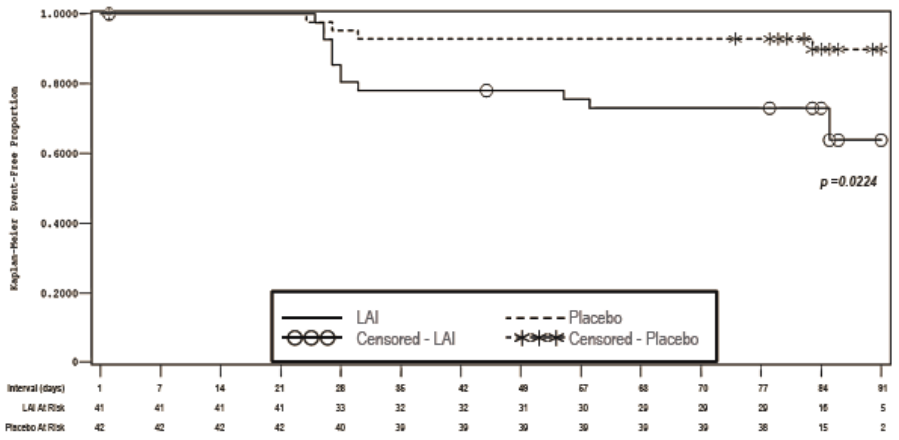
Inhaled Liposomal Amikacin

Proportion of Subjects with NTM Culture Conversion to Negative (mITT Population)



NOTE: Missing Values Excluded
P-value for stratified Cochran-Mantel-Haenszel test of treatment arm adjusting for the randomization strata

Kaplan-Meier Plot of Time from Study Baseline to NTM Culture Negative* (mITT Population)



* Censoring at Date of Last Contact or At Initiation of Open-Label LAI

Note: Subjects without event or censoring criteria are censored at study day 91.
Number at risk is the subjects remaining at risk after the corresponding interval day.

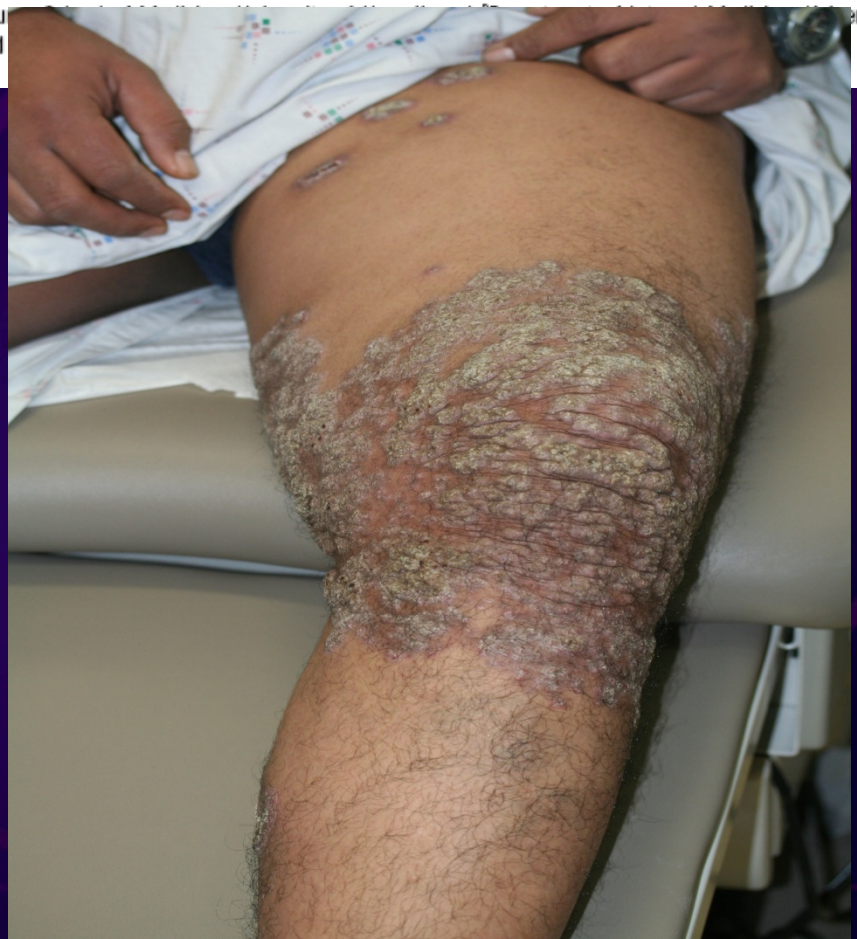
Olivier K et al. ATS 2014

Pulmonary Hygiene

Sequelae of World War II: An Outbreak of Chronic Cutaneous Nontuberculous Mycobacterial Infection among Satowanese Islanders

Joseph V. Lillis,[1] Vernon E. Ansdell,[8,9] Kino Ruben,[10] Eric L. Simpson,[1] Gloria Tumbaga,[8] David Ansdell,[8] Samuel Bremmer,[2] Stephen E. Kurtz,[7] Clifton R. White, Jr.,[1,2] Andrew Blauvelt,[1,3,7] and Kevin L. Winthrop[4,5,6]

Departments of [1]Dermatology, [2]Pathology, [3]Molecular Microbiology and Immunology, [4]Infectious Diseases, [5]Ophthalmology, and [6]Public Health and Preventive Medicine, School of Medicine, Oregon Health and Science University, and [7]Dermatology Service, Veterans Affairs Medical Center, Portland, Oregon; [8]John A. Bu[illegible]-Permanente Medical Center, Honolulu, Hawaii; and



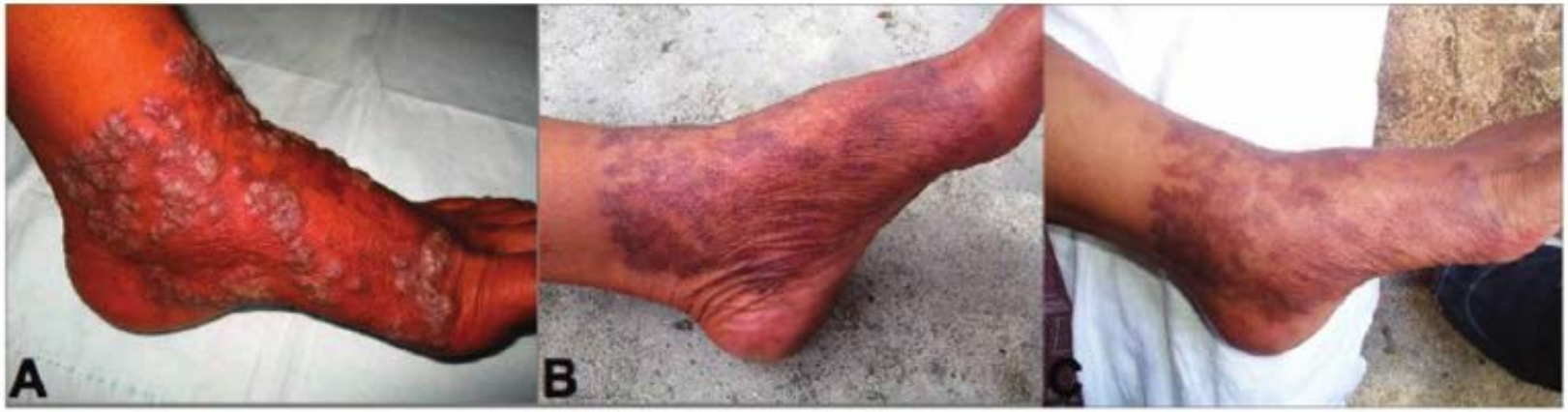
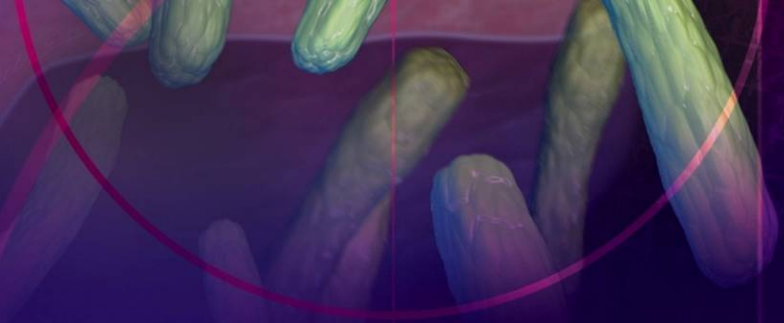
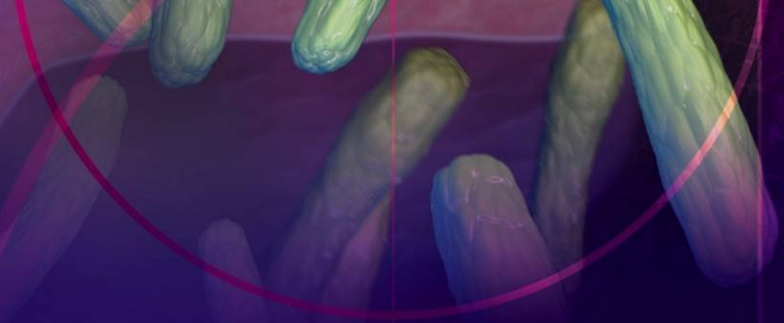


Figure 3. Clinical appearance before treatment *(A)*, after 3 months of treatment with doxycycline (100 mg twice a day) *(B)*, and at 9 months after treatment *(C)*.

Acknowledgements

- Close colleagues and friends at variety of institutions including:
  - NJMC, Mayo, UT Tyler, NIH, Univ. Ontario, U Florida, CDC, ATS/IDSA, OHSU, OHA, UAB, NTMir, COPD Foundation





Need Paradigm

- First-line therapeutic for MDR regimen
  - “Refractory” patients
  - “Treatment-naïve” patients
- Can we shorten treatment? Fewer drugs?
  - tolerability
- New treatment strategies
  - Suppressive
  - Post-treatment suppressive/preventive

Patient-centered research priorities

Topic	Priority	Potential specific questions and next steps
Quality of Life	6. Reduce the impact on patients of anxiety and depression	Evaluate anxiety and depression after diagnosis or during treatment in NTM patients Association between anxiety/depression and poorer treatment adherence
	7. Develop an NTM-specific Health-Related Quality of Life tool.	Validate NTM Symptom Module* tool
	8. Promote quality-of life measures for assessing the effectiveness of treatment	Validate correlation between NTM module and clinical outcomes
Treatment	**9. Reduce the burden of antibiotic treatment for NTM disease**	Develop and evaluate alternative delivery systems for IV antibiotics Repurpose existing therapies Develop new, more effective drugs with a shorter therapy duration
	10. Develop and test the efficacy of non-pharmacological therapies and holistic medicine approaches	Comparative effectiveness of exercise and lung clearance devices, taking into account ease of use and affordability
	11. Improve understanding of who needs or benefits from antibiotic therapy.	Role of therapy in mild cases to prevent disease progression Predictors of treatment response
Clinical outcomes	12. Develop a composite measure of disease activity or severity.	Develop a composite index of disease activity or severity that include microbiological, chest imaging, and quality of life measures.
	13. Identify and validate biomarkers associated with disease risk, prognosis, and treatment response	Identify biomarkers associated with disease risk, prognosis, or treatment response

Ann Am Thor Soc 2016

Immunosuppressive use common in Pulmonary NTM

TABLE 2. COMPARISON OF PULMONARY NTM DISEASE CHARACTERISTICS BETWEEN MALE AND FEMALE CASE SUBJECTS

	Female (*n* = 109)	Male (*n* = 75)
Age (median)	68 yr*	62 yr*
Cavitation†	22 (20%)	22 (31%)
Effusion	13 (12%)*	18 (24%)*
COPD	24 (22%)*	28 (37%)*
Bronchiectasis	22 (20%)	8 (11%)
Immunosuppressive Tx	32 (29%)	15 (20%)
Previous TB‡	8 (7%)	9 (12%)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; TB = tuberculosis; Tx = treatment.

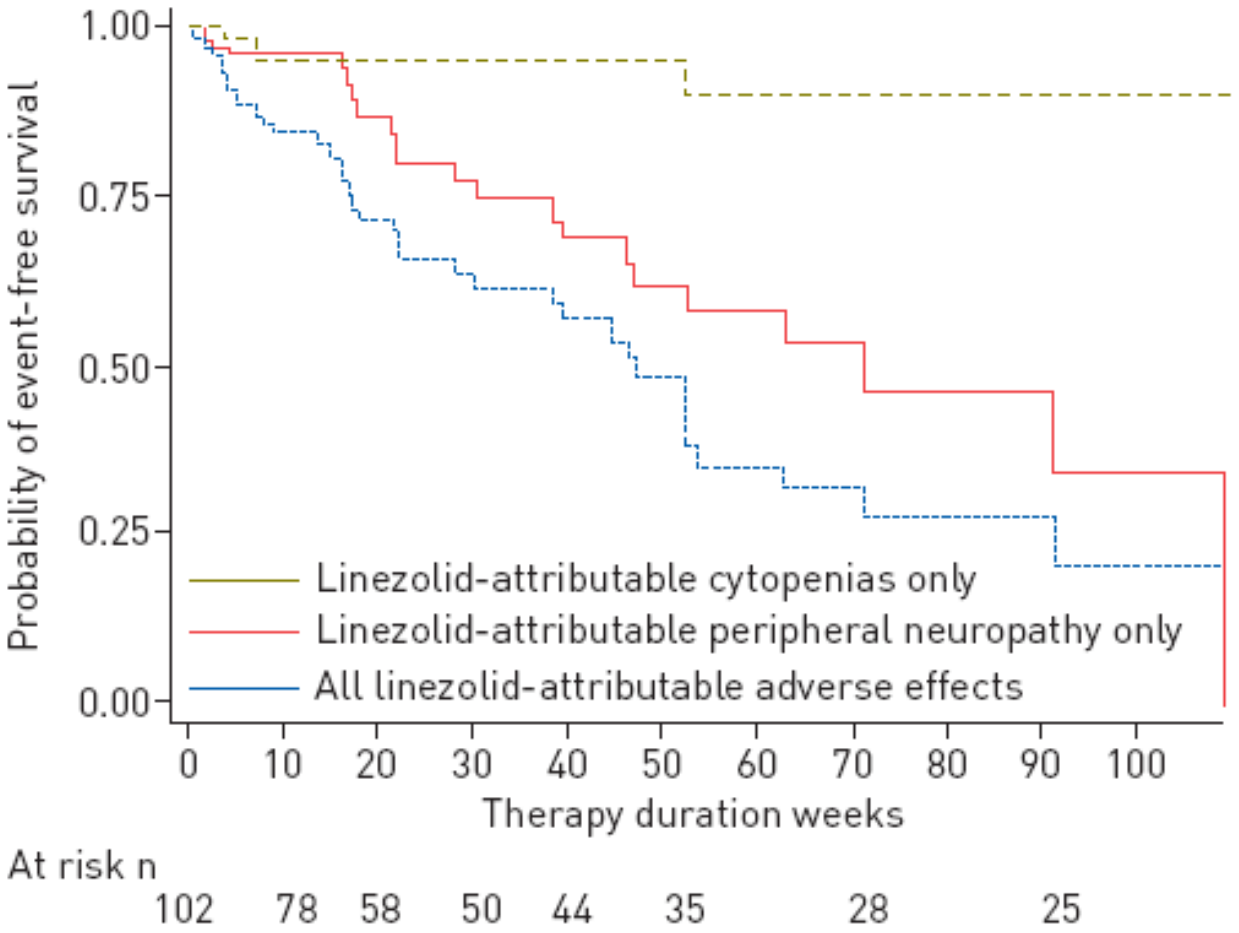
* Denotes $P < 0.05$ for comparison between columns designated male and female.

† Cavitation noted on either chest radiograph or computed tomography.

‡ Previous TB included history of latent TB infection (n = 11), prior active TB disease (n = 3), and history of unknown active versus latent TB (n = 3).

Winthrop et al. *AJRCCM* 2010

Discontinuation Due to Linezolid-attributed Adverse Events



Winthrop KL et al. ERJ 2014

M. abscessus Therapy

- "Cure" = rare (often treat off and on forever)
- More rapidly progressive or relentless than MAC
- 3-4 drugs for 18-24 months
  - 4-6 months "induction" phase
  - "suppressive strategy" thereafter
- Rotational parenteral based regimen

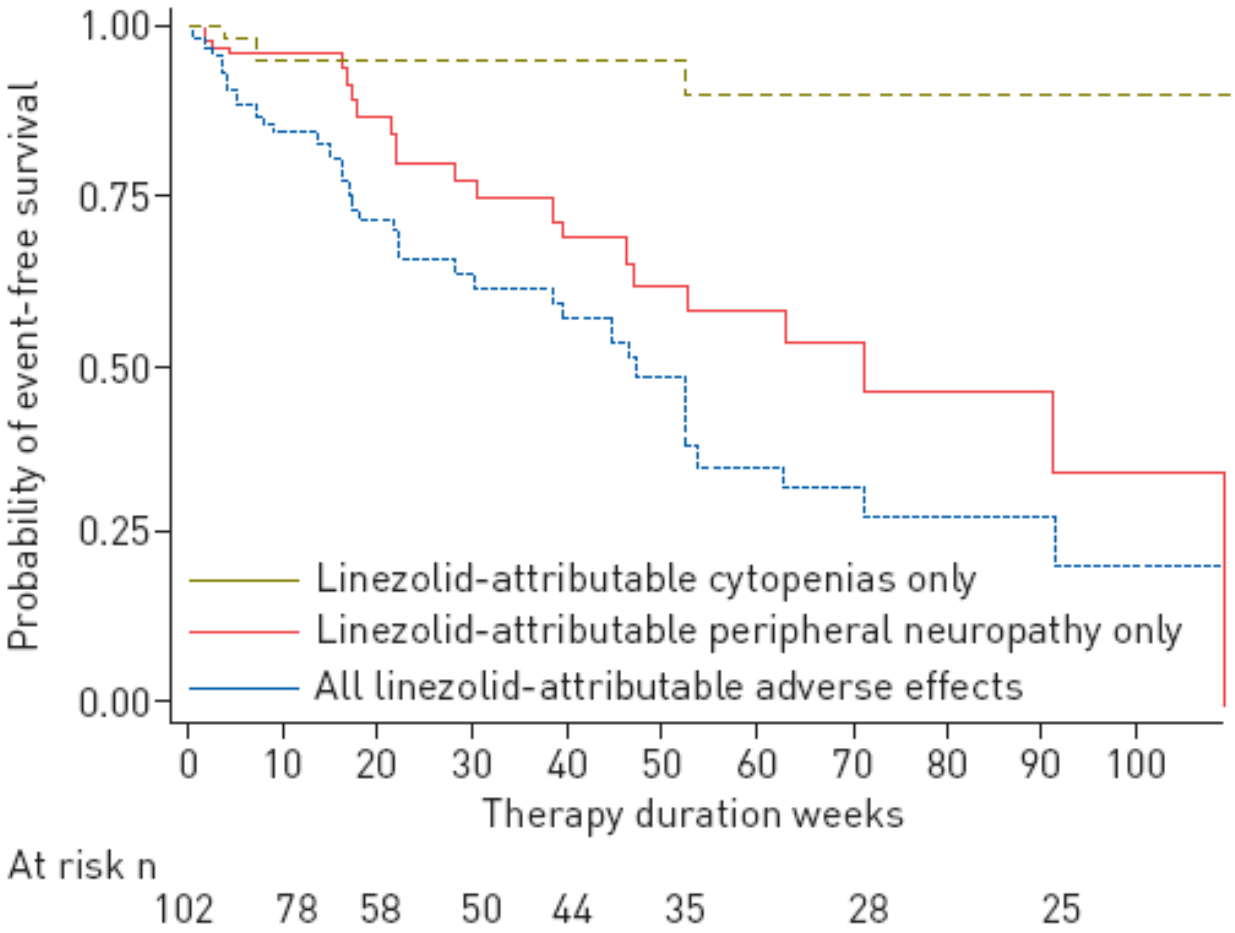
Clofazimine

- Must get from FDA
  - Investigational New Drug application
- Leprosy and MDR-TB
- NTM?
  - Experience in HIV patients with MAC
  - Immunosuppressive versus antimicrobial effects
  - Possible synergism with amikacin
  - GI intolerance and reversible tan
- FDA R01 for placebo-controlled RCT with non-cavitary MAI

Linezolid

- Drug developed for Staph (MRSA) and other gram positives
  - Has anti-mycobacterial activity
  - NTM efficacy unknown
- 600mg once daily
- 100mg B6
  - Cytopenias
  - Peripheral neuropathy
  - Optic neuritis

Discontinuation Due to Linezolid-attributed Adverse Events



Winthrop KL et al. ERJ In Press

TREATMENT EPISODES WITH INITIAL* INTERMITTENT OR DAILY MACROLIDE/AZALIDE-BASED THERAPY FOR NODULAR-BRONCHIECTATIC (NB) MAC LUNG DISEASE

	TIW** No. (%)	Daily No. (%)	Combined TIW/Daily No. (%)	P value
Regimen Modification*				
Clarithromycin	3/74 (4%)	14 /21 (67%)	17/95 (18%)	0.0001†
Azithromycin	2/72 (3%)	10/13 (77%)	13/85(15%)	0.0001†
Clari + Azi	5/180 (3%)	24/34 (71%)	40/339 (12%)	0.001†
Sputum Conversion§				
Clarithromycin	75/87 (86%)	3/4 (75%)	78/91 (86%)	0.1‡
Azithromycin	72/85 (85%)	4/4 (100%)	76/89 (85%)	
Clari + Azi	147/172 (85%)	7/8 (88%)	154/180 (86%)	

Plus-minus values are mean ± SD.

* Macrolide/azalide given at the initiation of treatment.

**TIW = three times weekly or Monday-Wednesday-Friday

† TIW vs Daily therapy

§ Macrolide/azalide given at the completion of therapy

‡ Clarithromycin-containing regimen vs azithromycin-containing regimen

Wallace R, et al *Chest* 2014

MICROBIOLOGIC RESULTS FOR ALL PATIENTS WITH CLARITHROMYCIN AND AZITHROMYCIN-CONTAINING REGIMENS*

	Clarithromycin	Azithromycin	Total	P value
No. Patients	91	89	180	
Sputum Conversion- no. (%)	78/91 (86%)	76/89 (85%)	154/180 (86%)	0.4**
Days to Convert	130.6 ± 149.7	123.2±109.8		0.7**
Months Negative Cultures On Therapy	12.1 ± 2.5	12.6 ± 3.5		0.3**
Treatment Duration (months)	18.6 ± 8.8	18.8 ± 6.3		0.9**
Microbiologic Recurrence On Therapy ‡- no. (%)§	14/91 (15%)	11/89 (12%)	25/180 (14%)	0.4**
Microbiologic Recurrence Off Therapy ‡- no. (%)‡	41/77 (53%)	33/78 (42%)	74/180 (48%)	0.6**
Months Microbiologic Follow-up Off Therapy	44.1 ± 31.4	40 ± 25.5		0.1
Months Clinical Follow-up Off Therapy	44.4 ± 31.3	40.7 ± 27.1		0.2

Plus-minus values are mean ± SD.

* Macrolide/azalide given at the completion of treatment.

** Clarithromycin-containing regimen vs azithromycin-containing regimen

§ Microbiologic Recurrence: ≥2 positive sputum AFB cultures for MAC after sputum conversion on therapy.

‡ Microbiologic Recurrence: ≥2 positive sputum AFB cultures for MAC after successful completion of therapy.

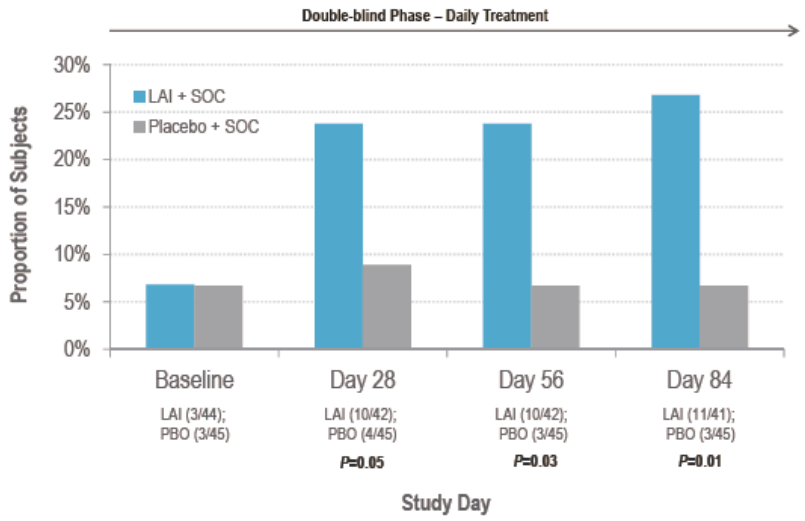
Wallace R, et al *Chest* 2014

Other Adverse Events

- Ethambutol
  - Optic neuritis, hair loss
- Rifampin
  - Hepatotoxicity, red urine/tears, thrombocytopenia, drug interactions, interstitial nephritis, cytopenias
- Rifabutin
  - Uveitis, flu-like syndrome, arthralgia, cytopenias
- Macrolides
  - Foul taste, tinnitus, hearing decline, sudden cardiac death
- Cefoxitin
  - Neutropenia, renal failure, rash
- Quinolones
  - QT prolongation, tendinopathy, CNS (insomnia, delerium)

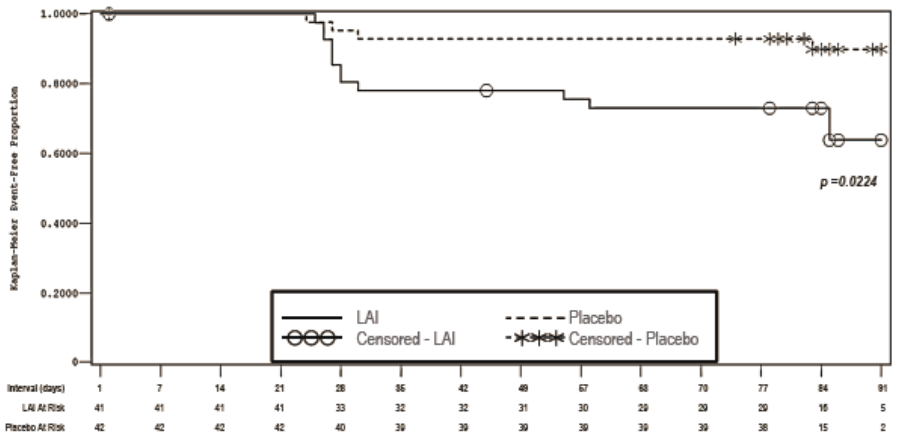
Inhaled Liposomal Amikacin

Proportion of Subjects with NTM Culture Conversion to Negative (mITT Population)



NOTE: Missing Values Excluded
P-value for stratified Cochran-Mantel-Haenszel test of treatment arm adjusting for the randomization strata

Kaplan-Meier Plot of Time from Study Baseline to NTM Culture Negative* (mITT Population)



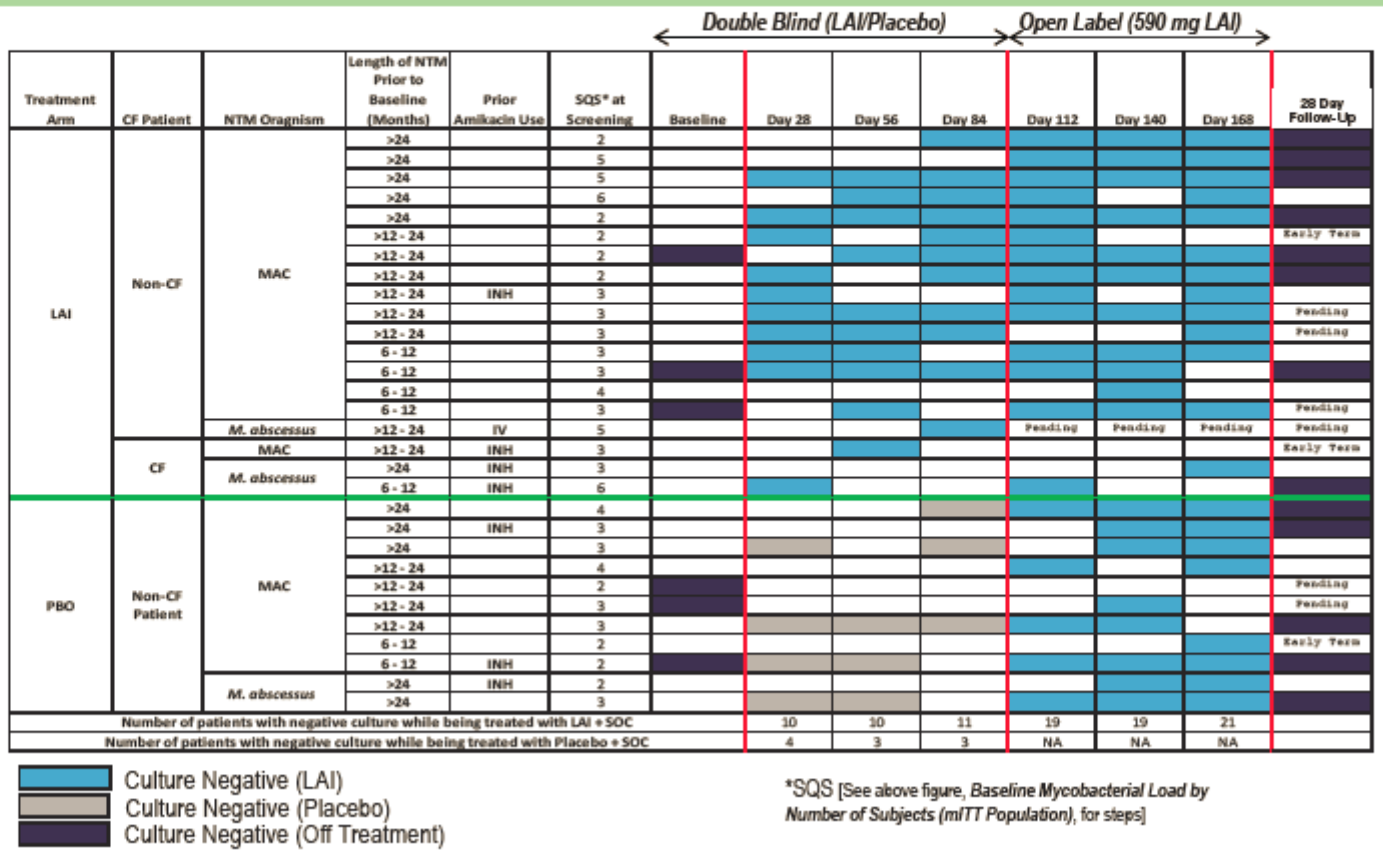
* Censoring at Date of Last Contact or At Initiation of Open-Label LAI

Note: Subjects without event or censoring criteria are censored at study day 91.
Number at risk is the subjects remaining at risk after the corresponding interval day.

Olivier K et al. ATS 2014

CULTURE CONVERSION

Data for Subjects with at least 1 Negative Culture Completing the Open Label Phase



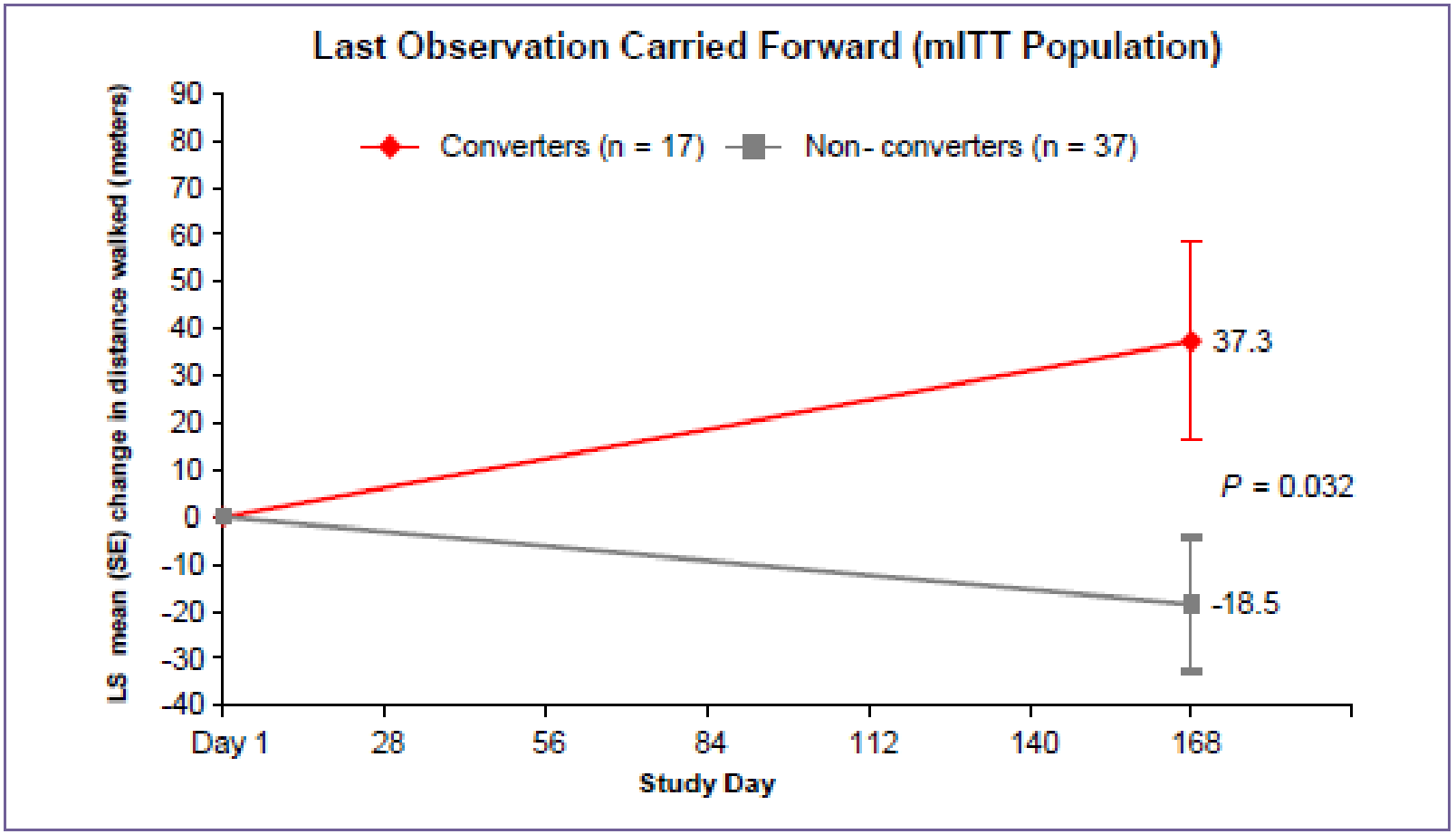
Treatment Arm	CF Patient	NTM Oragnism	Length of NTM Prior to Baseline (Months)	Prior Amikacin Use	SQS* at Screening	Baseline	Day 28	Day 56	Day 84	Day 112	Day 140	Day 168	28 Day Follow-Up
LAI	Non-CF	MAC	>24		2								
			>24		5								
			>24		5								
			>24		6								
			>24		2								
			>12 - 24		2								Early Term
			>12 - 24		2								
			>12 - 24		2								
			>12 - 24	INH	3								
			>12 - 24		3								Pending
			>12 - 24		3								Pending
			6 - 12		3								
			6 - 12		3								
			6 - 12		4								
			6 - 12		3								Pending
		M. abscessus	>12 - 24	IV	5					Pending	Pending	Pending	Pending
	CF	MAC	>12 - 24	INH	3								Early Term
		M. abscessus	>24	INH	3								
			6 - 12	INH	6								
PBO	Non-CF Patient	MAC	>24		4								
			>24	INH	3								
			>24		3								
			>12 - 24		4								
			>12 - 24		2								Pending
			>12 - 24		3								Pending
			>12 - 24		3								
			6 - 12		2								Early Term
			6 - 12	INH	2								
		M. abscessus	>24	INH	2								
			>24		3								
Number of patients with negative culture while being treated with LAI + SOC							10	10	11	19	19	21	
Number of patients with negative culture while being treated with Placebo + SOC							4	3	3	NA	NA	NA	

*SQS [See above figure, *Baseline Mycobacterial Load by Number of Subjects (mITT Population)*, for steps]

Note: All negative cultures confirmed with no growth in liquid medium

Olivier K et al. ATS 2014

Figure 5. Mean change in distance walked (meters) in the 6MWT in patients with non-CF MAC infection with culture conversion (≥3 negative cultures) vs. those without culture conversion (Day 168)



6MWT, six-minute walk test; CF, cystic fibrosis; LS, least squares; MAC, *Mycobacterium avium* complex; mITT, modified intent-to-treat.

Winthrop K et al, ATS 2015 abstract

NTM Disease Manifestations

Table 2. Nontuberculous mycobacterium (NTM) cases by species and disease site, Oregon 2007-2012

Mycobacterium species	Pulmonary	Skin/ soft tissue	Disseminated	Lymph	Other	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
M. avium/intracellulare complex	1005 (92.8%)	68 (37.8%)	35 (79.5%)	21 (87.5%)	42 (60%)	1171 (83.6%)
M. abscessus/chelonae complex	46 (4.2%)	51 (28.3%)	1 (2.3%)	1 (4.2%)	9 (12.9%)	108 (7.7%)
M. fortuitum/ mucogenicum	5 (0.5%)	21 (11.7%)	2 (4.5%)	1 (4.2%)	3 (4.3%)	32 (2.3%)
M. marinum	-	17 (9.4%)	-	-	2 (2.9%)	19 (1.4%)
M. lentiflavum	6 (0.6%)	1 (0.6%)	-	-	-	7 (0.5%)
M. kansasii	5 (0.5%)	-	-	-	1 (1.4%)	6 (0.4%)
M. bovis	-	1 (0.6%)	-	-	3 (4.3%)	4 (0.3%)
M. goodii	-	4 (2.2%)	-	-	-	4 (0.3%)
M. xenopi	2 (0.2%)	1 (0.6%)	-	-	1 (1.4%)	4 (0.3%)
M. aubagnense	-	1 (0.6%)	1 (2.3%)	-	1 (1.4%)	3 (0.2%)
M. alvei	-	2 (1.1%)	-	-	-	2 (0.1%)
M. immunogenum	1 (0.1%)	-	-	-	1 (1.4%)	2 (0.1%)
Other (unspeciated and 13 species with a single case)	13 (1.2%)	12 (6.7%)	5 (11.4%)	1 (4.2%)	7 (10%)	38 (2.7%)
TOTAL	1083	180	44	24	70	1401

77% of NTM disease is pulmonary

Henkle E, et al. (abstract) ATS 2014

Immunosuppression and NTM

- More frequently disseminated
  - Local inoculation versus GI route

<u>Risk factors and conditions</u>

- ESRD, prednisone, biologic immunosuppressives
- HIV
- Cancer, transplant, leukemia (hairy cell)
- Auto-antibody and cytokine/receptor deficiency states
  - INF-gamma, IL12-23 pathway, STAT-1

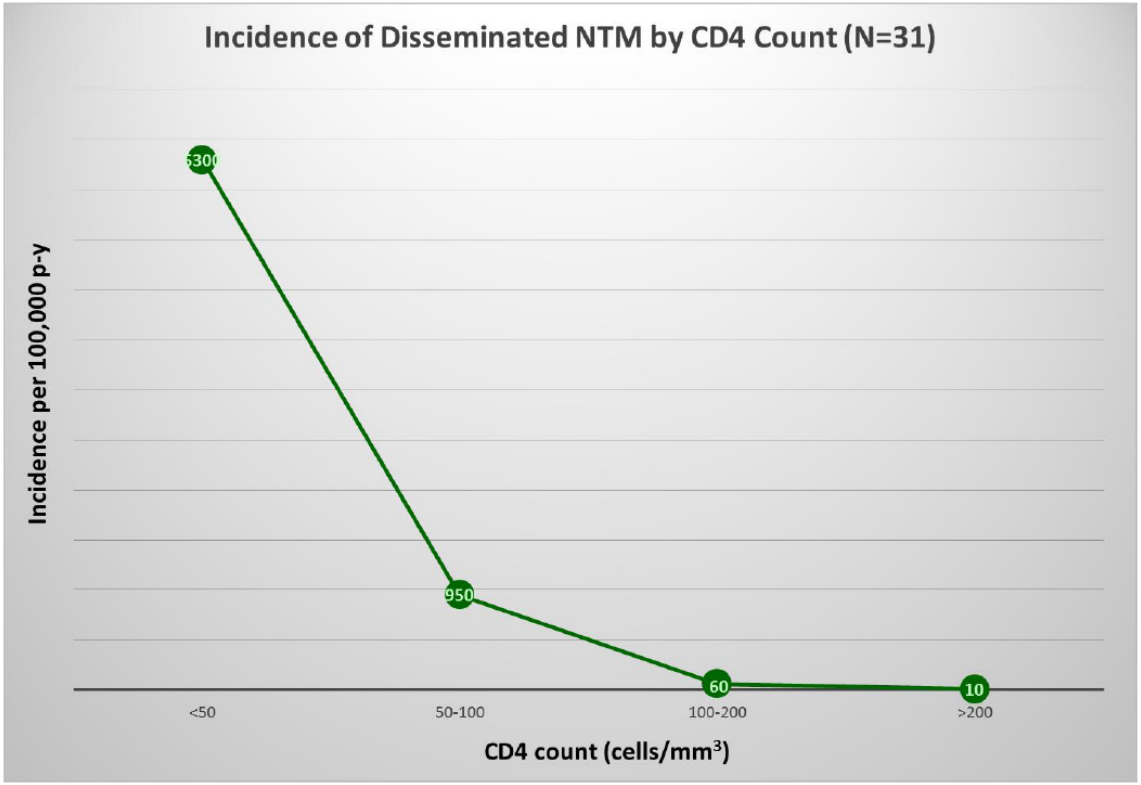
- Disease split between RGM and slow growers
  - RGM more common here than in pulmonary disease

Tofacitinib and "Opportunistic" Infections (P2P3LTE)

- 60 OIs reported (IR 0.46/100 pys [0.36-0.59])
  - TB (n=26)
  - PCP (n=4)
  - CMV (n=6)
  - Candida Esophagitis (n=9)
  - Cryptococcus (n=3)
  - Pulmonary NTM (n=2)
  - HZ, multi-dermatomal (n=8)
  - BK encephalopathy (n=1)
  - Toxoplasmosis (n=1)

Winthrop K et al. ARD 2015

Disseminated MAC in HIV



Incidence by CD4 Count Closest to Disseminated NTM Diagnosis Date (cells/mm³) per 100,000 p-y (95% Poisson Confidence Interval)

< 50	50-100	100-200	> 200
5300	950	60	10
(3360-7950)	(310-2210)	(0-310)	(0-30)

Varley C et al. IDSA abstract 2015

Tigecycline

- Efficacy unknown
  - Disease stabilization
- Use limited by severe nausea and vomiting
  - CF kids versus elderly
- 50mg once daily
  - Pre-treat zofran or other anti-emetic

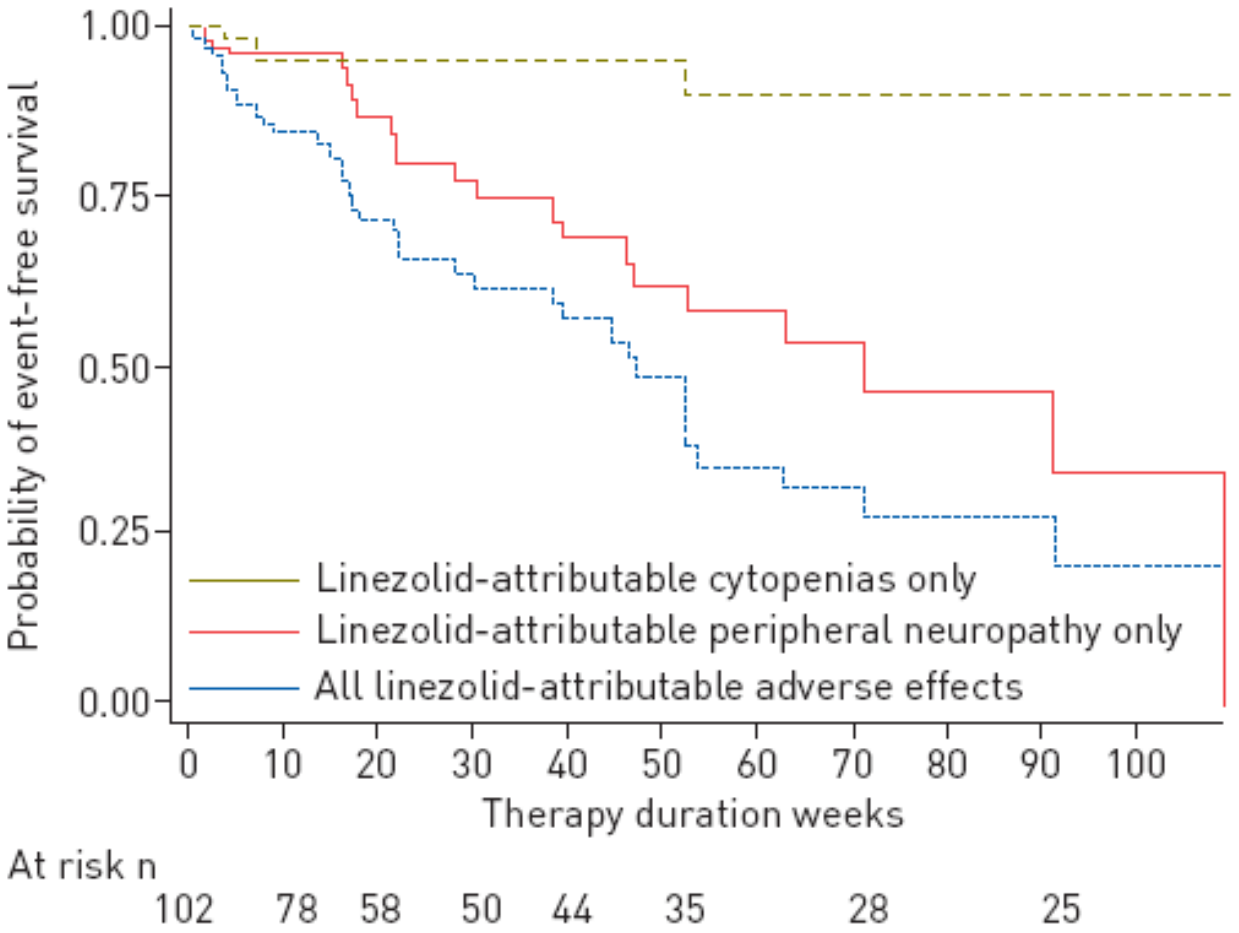
Clofazimine

- Must get from FDA
  - Investigational New Drug application
- Leprosy and MDR-TB
- NTM?
  - Experience in HIV patients with MAC
  - Immunosuppressive versus antimicrobial effects
  - Possible synergism with amikacin
  - GI intolerance and reversible tan

Linezolid

- Drug developed for Staph (MRSA) and other gram positives
  - Has anti-mycobacterial activity
  - NTM efficacy unknown
- 600mg once daily
- 100mg B6
  - Cytopenias
  - Peripheral neuropathy
  - Optic neuritis

Discontinuation Due to Linezolid-attributed Adverse Events



Winthrop KL et al. ERJ 2014

IRIS

- Similar phenomenon as seen with TB (or other opportunistic infection)
- Incidence is variable
  - 5% of TNF-associated NTM cases
- Diagnosis of exclusion
- Can be clinically devastating
- Management with high dose prednisone
  - Anti-TNF therapy if needed

Winthrop K et al. CID 2008; Wallis R et al CID 2009

Drug-Drug Interactions

- Rifampin
  - Beta-blockers, Levothyroxine, CA2+ blockers, warfarin
  - Tacrolimus, steroids, cyclosporin
  - Azoles, Protease inhibitors, FQs
- Azithromycin
  - Digoxin, warfarin
- Clarithromycin has many of the above
- QT issue
  - Clari/azi, FQs, Bedaquiline, Clofaz, others

Patient-centered research priorities

- PCORI Eugene Washington Meeting Award
- 1-day meeting in November 2015
- 24 patients, caregivers, patient advocates, clinical experts, researchers
- Pre-meeting surveys: patient/advocate and clinical/research

Step 1: Formulate your question

- **Begin by formulating your question using the PICO format:**
  - **P: Population**
  - **I: Intervention**
  - **C: Comparator**
  - **O: Outcomes**

Assess the quality of evidence

- **The "quality of evidence" is the confidence that you have in the results of the studies**

Quality of evidence	Suggested implications
High	further research is unlikely to change the confidence in an estimated effect
Moderate	further research is likely to have an important impact on the confidence in an estimated effect
Low	further research is very likely to have an important impact on the confidence in an estimated effect and is likely to change that estimate
Very low	any estimate of an effect is very uncertain

New ATS/IDSA NTM guidelines

- Systematic reviews are finished
- Data reviewed
- Currently in drafting

- What I've learned
  - WE NEED MORE FUNDED RESEARCH

Patient-centered research priorities

Topic	Priority	Potential specific questions and next steps
Prevention	1.Strengthen the role of patients in preventing NTM infection or reinfection	Evaluate whether aspiration increase the risk of NTM infection or reinfection
	2. Limit the risk of patient-to-patient transmission of NTM infection in cystic fibrosis clinics.	Estimate the risk of person-to-person or indirect transmission in CF clinics Comparative effectiveness of standard and expanded infection control precautions
Diagnosis	3. Improve the timeliness of diagnosis and develop molecular techniques for rapid species identification and susceptibility	Validate molecular diagnosis techniques being developed by National Jewish Healthcare
	4. Develop a screening algorithm for patients at risk for pulmonary NTM disease	Predictors of positive culture Predictors of meeting ATS disease criteria at diagnosis
	5. Develop better methods for sputum collection and testing	Identify techniques that improve sputum collection Develop new collection devices